MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Date: January 14, 2010

To: Lori Tull, CSO, OCTGT/RMS
Thomas Finn, PhD, Chairperson, OCTGT/DCGT
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From: Catherine A. Miller, CSO
Advertising and Promotional Labeling Branch (APLB)

Through: Ele Ibarra-Pratt, RN, MPH
Branch Chief, APLB

Subject: Preliminary comments on draft product and patient labeling
Provenge (sipuleucel-T)
BLA STN 125197

Dendreon submitted a draft package insert (PI) and patient package insert (PPI) to BLA STN 125197 on October 30, 2009 for Provenge (sipuleucel-T). APLB offers the following comments on the draft PI and PPI.

GENERAL

Use command language whenever possible.

HIGHLIGHTS

Drug Name, Dosage Form, and Route of Administration

For biological products, the dosage form should be on the line underneath the proper name. An SPL acceptable term is "Suspension for Injection." Because the route of administration is not typical for this dosage form, we suggest that a third line be added with the route of administration, "For Intravenous Infusion."

Indications and Usage

The class of the product should be included in the indication. For example, "Provenge is an autologous cellular immunotherapy product indicated for the treatment of metastatic castrate (hormone refractory) prostate cancer." It is unnecessary to include "men" in the indication.

Dosage and Administration

The bolded statement "For Intravenous Use Only" should appear directly beneath the header of this subsection.

We recommend that the sequence of bullets be revised to the sequence of preparation and administration. In addition, the bullets can be simplified for better comprehension. For example:

- Premedicate patients with oral acetaminophen and an antihistamine such as diphenhydramine.
- Administer 3 doses at 2-week intervals.
- Infuse Provenge intravenously over a 60 minute period. **Do not use a cell filter**.
- Interrupt or slow infusion for acute infusion reactions.

Dosage Forms and Strengths

We recommend that you revise this subsection for ease of comprehension to "250 mL suspension containing a minimum of 50 X 10^6 autologous $CD54^+$ antigen presenting cells."

Contraindications

Please revise the statement to "None."

Warnings and Precautions

Please list the items in this section in decreasing order of importance. For example, acute infusion reactions have been observed in patients and should be listed before the theoretical risk of viral transmission.

Are there other warnings or precautions from the clinical trials that should be included in this section, e.g., sepsis or infections? Patients discontinued treatment in the study as a result of sepsis.

Revision Date

Please include "Revision date" with the month and year that the application is approved at the end of Highlights.

FULL PRESCRIBING INFORMATION

Indications and Usage

The class of the product should be included in the indication. For example, "Provenge is an autologous cellular immunotherapy product indicated for the treatment of metastatic castrate (hormone refractory) prostate cancer." It is unnecessary to include "men" in the indication.

Dosage and Administration

Please add "For Intravenous Use Only" directly beneath the header and "Infuse the entire volume of the bag" under "Administration."

Consider reordering this section to be consistent with the order of administration, for example:

2.1 Dose and Schedule
2.2 Pre-dose Leukapheresis
2.3 Premedication

2.4 Administration
2.5 Dose Modification for Infusion Reactions

Dosage Forms and Strengths

We recommend that you revise this subsection to "250 mL suspension containing a minimum of 50 X 10^6 autologous $CD54^+$ antigen presenting cells."

Warnings and Precautions

Please list the warnings and precautions in decreasing order of importance. For example, acute infusion reactions have been observed in patients and should be listed before the theoretical risk of viral transmission.

Please delete "Provenge is designed to activate the immune system" from subsection 5.1 "Concomitant Chemotherapy or Immunosuppressive Therapy" because it is promotional. Subheadings should identify the content of the subsection. Please revise the subheading "General Precautions" to one that identifies the content as the lack of final sterility test results.

Are there other warnings or precautions from the clinical trials that should be included in this section, e.g., sepsis or infections? Patients discontinued treatment in the study as a result of sepsis.

Adverse Reactions

Please list the common overall adverse reactions directly beneath the section header using a cut-off frequency.

Adverse reactions should be presented in an easy-to-follow order (e.g., body system). For detailed advice on revising this section, please see Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and biological Products – Content and Format.

Drug Interactions

The claim "There have been no reports of drug interactions associated with the administration of Provenge" is misleading and promotional. We recommend revising this section to "No drug interaction studies have been conducted."

Description

The claim "Provenge is an autologous active cellular immunotherapy product designed to stimulate an immune response against **prostate cancer**" (emphasis added) may suggest that Provenge is indicated for all prostate cancers rather than metastatic castrate resistant (hormone refractory) prostate cancer. We recommend that you revise this claim to specifically state "metastatic castrate resistant (hormone refractory) prostate cancer."

Clinical Pharmacology/Mechanism of Action

This section should include only established mechanism(s) of actions in humans. Delete theoretical discussions and exploratory analyses.

Clinical Studies

General Comments

Please delete "primary" and "secondary" in reference to the endpoints.

Please delete "Phase 3" when describing the studies.

Please delete the internal company study titles (e.g., D9902B, IMPACT Study, D9901, and D9902A) and title the studies as "Study 1," Study 2," etc.

IMPACT Study (D9902B)

The claim "The clinical benefit of Provenge as measured in the intent-to-treat population demonstrated that patients treated with Provenge had a statistically significant survival advantage compared with placebo" in the fourth paragraph is promotional. We recommend deleting this claim and simply presenting the data.

Please include n for the 36-month survival to provide context for the percentages.

Delete subgroup analyses that are not pre-specified.

Study D9901

It is important to show the absolute difference between treatment groups for the endpoint of time to disease progression. Please include these data.

The median survival times in study D9902B are very similar to the median survival times in study D9901; however, Dendreon claims 22.5% reduction in the risk of death for study D9902B and a 41% reduction in the risk of death in study D9901. Please verify the accuracy of these values for reduction in the risk of death.

Study D9902A

It is important to show the absolute difference between treatment groups for the endpoint of time to disease progression. Please include these data.

IMPACT Study (D9902B), Study D9901, Study D9902A, and Table 5

Please include 'n' for the 36-month survival to provide context for the percentages. For example, "The number of patients alive at 3 years by Kaplan Meier estimate was 109 (32%) in the Provenge arm compared with 39 (23%) in the placebo arm."

Patient Counseling Information

We recommend that this section be revised to command language. This section is intended to assist in discussion between the healthcare provider and the patient or caregiver. It should not be a recap of the prescribing information and does not need subsections. For example

Inform the patient or caregiver about the following:

- The recommended course of therapy for Provenge is 3 complete doses. It is important to maintain all scheduled appointments and arrive at each appointment prepared and on time because Provenge expiration times must not be exceeded and the infusions must be appropriately spaced.
- If the patient is unable to receive an infusion of Provenge, the patient will need to undergo additional leukapheresis procedure(s) if the course of treatment is to be continued.
- Preparation instructions for the leukapheresis procedure and the possible side effects, including nutritional recommendations and hydration requirements, as well as post-procedure care.
- If the patient does not have adequate peripheral venous access to accommodate the leukapheresis procedure, inform the patient about the need for a central venous catheter for leukapheresis and infusion of Provenge. Counsel the patient on the importance of catheter care. Instruct the patient to tell their doctor if they are experiencing any unexplained fevers because fevers could be a sign of an infected catheter.
- Report signs and symptoms of acute infusion reactions such as fever, chills, breathing problems, nausea, vomiting, headache, or muscle aches.
- Report any symptoms suggestive of a cardiac arrhythmia.
- Inform their doctor if they are taking immunosuppressive agents.
- PSA measurements may not necessarily reflect response to treatment with Provenge.

Patient labeling is not a subsection of this section, although it is printed immediately following this subsection. Include the patient labeling at the end of this section, but do not number it as a subsection.

Patient Labeling

General Comments

Patient information (PPI) should always be consistent with the prescribing information (PI). All future relevant changes to the PI should also be reflected in the PPI.

The patient labeling should use simple sentences and command language wherever possible. Bullets help in the comprehension of patient labeling. Refrain from describing practice of medicine and the use of descriptors such as “rare” that cannot be quantified.

Title

Include the phonetic spelling of the name, Provenge, with the emphasized syllable in all capitals, on the same line as the brand name.

The words “therapy” and “treatment” are used interchangeably. It is better to use one word consistently to avoid confusion. Please revise the first sentence to “This leaflet is designed to help you understand treatment with Provenge.”

What is Provenge?
We recommend revising this section to simply state "Provenge is a prescription medicine that is used to treat certain advanced prostate cancers. Provenge is made by mixing some of your own immune cells with a certain protein." Please delete promotional claims such as "Provenge is designed to…target and attack prostate cancer."

What is in Provenge?
Please delete this section since the information is now included in "What is Provenge?"

What should I tell my doctor before getting Provenge?
Revise this section to command language. For example

Tell your doctor about all your medical problems including

- Heart problems
- Lung problems
- History of stroke

Tell your doctor about all of the medicines you take including prescription and non-prescription drugs, vitamins, and dietary supplements.

How will I get Provenge?
Please revise this section to the following:

Since Provenge is made from your own immune cells, your cells will be collected 2 to 3 days before each scheduled infusion of Provenge. You will need to go to a blood bank or apheresis center for this collection. The collection is called "leukapheresis" [please provide the phonetic spelling of leukapheresis.]. Your collected cells are sent to a special lab where they are mixed with protein to make them ready for your infusion.

You will get Provenge in 3 intravenous infusions (put into your veins) about 2 weeks apart. Each infusion takes about 60 minutes.

Your doctor will give you a schedule for your cell collection and infusion appointments. It is very important that you keep your appointments. If you miss an appointment and can not be infused, your Provenge dose may not be usable. Your doctor will work with you to schedule a new appointment at the blood bank or apheresis center. You may also get a new infusion appointment.

A section entitled "**What are the possible or reasonably likely side effects of Provenge?**" should follow the section "How will I get Provenge?" For example,

What are the possible or reasonably likely side effects of Provenge?
The most common side effects with Provenge include

- chills
- fever
- headache
- muscle aches
- flu-like symptoms
- sweating

> Provenge infusion can cause serious reactions. Tell your doctor right away if you have breathing problems, chest pains, racing heart or irregular heartbeats, nausea or vomiting after getting Provenge because this may be a sign of heart or lung problems.
>
> Tell your doctor right away if you get a fever over 100ºF, redness or pain at the infusion or collection sites because this may be a sign of infection.
>
> Tell your doctor about any side effect that concerns you or does not go away.
>
> These are not all the possible side effects of Provenge treatment. For more information, talk with your doctor.

Please include a section titled "**What are the ingredients in Provenge?**" and include the active ingredients and inactive ingredients on separate lines.

Please delete the following sections:
What is in Provenge?
How is Provenge designed to work?
How do I get started?
What happens if I miss an appointment or my product cannot be infused?
What will happen to my PSA level when I receive Provenge?
What is leukapheresis?
What are the possible side effects of the leukophoresis procedure required to manufacture Provenge?
General Information

Delete the reference to the website www.provenge.com. This is not a regulated website and cannot be approved as part of the approved labeling for the product.

Include the name and address of the manufacturer.

The FDA MedWatch number may be included. If it is, state "Call our doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088."

The above preliminary comments have been provided from a comprehension and promotional perspective. If you have any questions regarding this review please contact Catherine Miller, Consumer Safety Officer, at 301-827-3028.

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bcc: HFM-602 C. Miller
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HFM-602 APLB Historical File

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